REMARKS

The invention features the cloning of mammalian methionine synthase reductase. Accordingly, the invention provides wild-type and mutant mammalian methionine synthase reductase nucleic acids.

Examination of claims 1-8 is reported in the present Office Action. In view of Applicant's election of the claims of Group 1, claims 9-34 have bee canceled without prejudice. Claims 1-8 were rejected under 35 U.S.C. § 112, second paragraph, and claims 1-8 were rejected under 35 U.S.C. § 112, first paragraph. Claims 4-6 were rejected under 35 U.S.C. § 102(b); claims 4-8 were rejected under 35 U.S.C. § 102(a), and claim 1 was rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed below in the order that they appear in the Office Action.

Support for the Amendment

Amendments have been made to more clearly recite the invention the applicants intent to claim. Support for the amendments to claim 3 and 4 and support for new claim 35 is provided, for example, by page 5, lines 17-18, and page 6, lines 1-11, of the specification. Support for new claims 36-44 is provided throughout the specification (see, for example, page 6, lines 1-11, and page 18). Support for new claims 45 and 46 is provided, for example, by page 16, lines 2-18, of the specification. Support for new claim 47 is provided, for example, by page 28, lines 10-13, and page 29, lines 19-25, of the specification and by Figures 2, 4, and 7. No new matter is added by these amendments.

Drawings

Applicants note that the Examiner has indicated that the drawings do not comply with the requirements for formal drawings. Once the application is deemed to be otherwise in condition for allowance, formal drawings will be submitted. Accordingly, this objection can now be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-8 stands rejected under § 112, second paragraph, as being indefinite for failure to distinctly claim the subject matter which applicants regard as the invention. In particular, the Examiner states that claims 4-8 are indefinite for the use of the term "high stringency." As suggested by the Examiner, applicants have amended claim 4 (from which claim 5 depends) to indicate that the nucleic acid hybridization occurs in 2X SSC medium at 40°C (as stated on page 16, lines 19-20, of the specification). Claims 6-8 have been cancelled. Accordingly, this aspect of the rejection may be withdrawn.

The Examiner further states that claim 5-8 are indefinite for insufficient antecedent basis for the limitation "the nucleic acid encoding the methionine synthase reductase." Claim 5 has been amended to replace this limitation with "SEQ ID NO: 1 or SEQ ID NO: 41." In view of this amendment, this aspect of the rejection may be withdrawn.

Applicants note that claims 1-3 also clearly recite the invention that applicants intend to claim. In particular, claim 1 is directed to a substantially pure nucleic acid which encodes a mammalian methionine synthase reductase polypeptide. As recited in claim 2, the nucleic acid may encode a human polypeptide, and as recited in claim 3, the nucleic acid may have the polynucleotide sequence of SEQ ID NOs: 1, 41, 43, 45, or 47, or a degenerate variation thereof. Applicants further note that new claims 35-44 also distinctly claim nucleic acids based on their percent sequence identity to the mammalian methionine synthase reductase nucleic acid of SEQ ID NO: 1. Accordingly, this indefiniteness rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 2, and 4-8 were rejected under 35 U.S.C. § 112, first paragraph, for failure of the specification to convey possession of the scope of the claimed invention. The Examiner states that the specification only discloses two mammalian methionine

synthase reductase nucleic acids (SEQ ID NOs: 1 and 41) and fails to describe any identifying characteristics or properties of mammalian methionine synthase reductase nucleic acids. The Examiner further states that the specification only discloses a single species of the genus of nucleic acids that hybridize at high stringency to SEQ ID NOs: 1 or 41. Applicants respectfully disagree.

Rejection for failure to describe a sufficient number of mammalian methionine synthase reductase nucleic acids sequences

In addition to the disclosure of the human methionine synthase reductase nucleic acids SEQ ID NOs: 1 and 41, the specification discloses human methionine synthase reductase nucleic acids in which (i) a guanine is replaced by adenine at nucleotide position 110 (SEQ ID NO: 43), (ii) nucleotides 1675-1678 are deleted (SEQ ID NO: 47), or (iii) nucleotides 1726-1728 are deleted (SEQ ID NO: 45) (page 6, lines 1-10). The specification also describes numerous characteristics of mammalian methionine synthase reductase nucleic acids that enable one skilled in the art to identify additional mammalian methionine synthase reductase nucleic acids. As stated on page 28, lines 10-13, and page 29, lines 19-25 of the specification and as illustrated in Figures 2, 4, and 7, mammalian methionine synthase reductase nucleic acids are characterized by the regions encoding the consensus binding sites for FAD, FMN, and NADPH (new claim 47). In particular, primers containing consensus binding sites for FAD, FMN, and NADPH were used by applicants in the cloning of human methionine synthase reductase and can be used to isolate or identify additional mammalian methionine synthase reductase nucleic acids. For this analysis, primers containing any of the numerous polynucleotide sequences disclosed by the Applicants that encode a FAD, FMN, or NADPH binding site or any other polynucleotide sequence identified by one skilled in the art as encoding a FAD, FMN, or NADPH binding site may be used. Mammalian methionine synthase reductase nucleic acids may also be readily identified based on their sequence identity to SEQ ID

NOs: 1, 41, 43, 45, and 47 and based on the enzymatic activity of the encoded protein. For example, standard assays such as those disclosed by the applicants may be used to measure the ability of the encoded protein to generate cob(III)alamin-CH3 from the reductive methylation of cob(II)alamin or to increase methionine synthase activity by maintaining the cobalamin cofactor of methionine synthase in an active state (page 16, lines 2-5; page 34, and page 35).

Applicants' disclosure of multiple human methionine synthase reductase nucleic acids enables one skilled in the art to determine the sequence of any other human methionine synthase reductase nucleic acid. For example, the rapid techniques for amplifying and sequencing a methionine synthase reductase nucleic acid, or a segment thereof, using the suggested oligonucleotide primers in Table 1 or any other primer allow a skilled artisan to determine the polynucleotide sequence of methionine synthase reductase from a patient sample, such as fibroblast cells (pages 17 and 42).

Given the human methionine synthase reductase nucleic acid sequences provided by the applicants, one skilled in the art of molecular biology can also readily design PCR primers or probes to clone a representative number of mammalian methionine synthase reductase genes. As noted above, probes designed based upon binding sites for FAD, FMN, and NADPH, or any other probe (such as a partial or full length human methionine synthase reductase nucleic acid) may be used in routine methods to screen any mammalian nucleic acid library to identify additional mammalian methionine synthase reductase nucleic acids. For example, as stated on page 17, line 15, through page 18, line 1, of the specification:

> Probes or primers specific for methionine synthase reductase nucleic acid preferably will have at least 35% sequence identity, more preferably at least 45-55% sequence identity, still more preferably at least 60-75% sequence identity, still more preferably at least 80-90% sequence identity, and most preferably 100% sequence identity. Probes may be detectably-labelled, either radioactively, or non-radioactively, by methods well-known to those skilled in the art. Probes are used for methods involving nucleic acid hybridization, such as: nucleic acid sequencing, nucleic acid amplification by the polymerase chain reaction, single stranded

conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern hybridization, Northern hybridization, in situ hybridization, electrophoretic mobility shift assay (EMSA).

The inventive concept claimed by the applicants includes the surprising degree of identity between the mammalian (*e.g.*, human) and non-mammalian methionine synthase reductase genes (*e.g.*, *C. elegans* putative methionine synthase reductase) (page 49 and Figure 4). Given the conservation between regions of the human and *C. elegans* genes, one skilled in the art would appreciate that these regions will also almost certainly be conserved in other mammalian synthase reductase genes. Thus, there is a great level of predictability inherent in the practice of the invention. In fact, one skilled in the art would expect a higher degree of conservation among these regions between the human and other mammalian methionine synthase reductase genes than between the human and *C. elegans* genes. Thus, this aspect of the rejection should be withdrawn.

Rejection for failure to describe a multiple nucleic acids that hybridize to a mammalian methionine synthase reductase nucleic acid

In response to the Examiner's assertion that the specification only discloses a single species of the genus of nucleic acids that hybridize at high stringency to the methionine synthase reductase nucleic acids of SEQ ID NOs: 1 or 41, applicants note that the human methionine synthase reductase nucleic acids of SEQ ID NOs: 43, 45, and 47 hybridize to SEQ ID NOs: 1 and 41. Furthermore, one skilled in the art can use these sequences to design or isolate other nucleic acids that hybridize to SEQ ID NOs: 1 or 41. For example, numerous nucleic acids with substantial sequence identity to SEQ ID NOs: 1 or 41 can be generated by one skilled in the art. As amended, claim 4 requires that the nucleic acid which hybridizes to SEQ ID NOs: 1 or 41 contains a region complementary to a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism. To generate such a nucleic acid, a skilled artisan can use a partial or full length nucleic acid that is complementary to a mutant or polymorphic mammalian

methionine synthase reductase nucleic acid, such as SEQ ID NOs: 41, 43, 45, or 47, or any other polymorphic mammalian methionine synthase reductase nucleic acid identified using the methods of the present invention. Applicants further note that the nucleic acids recited in new claims 36-44 may be readily generated by one skilled in the art based on the indicated percent identity to SEQ ID NO: 1. Thus, this rejection should be withdrawn.

Claims 1-8 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner acknowledges that the specification is enabling for a nucleic acid encoding the methionine synthase reductase of SEQ ID NOs: 2 or 42, a nucleic acid hybridizing at high stringency to SEQ ID NOs: 1 or 41, a nucleic acid of SEQ ID NO:1 in which nucleotides 1675-1678 are deleted, and a nucleic acid of SEQ ID NO:1 in which nucleotides 1726-1728 are deleted. However, the Examiner asserts that the specification does not enable any mammalian or any human methionine synthase reductase nucleic acid, any degenerate variant of SEQ ID NOs: 1 or 41, or any nucleic acid that hybridizes at high stringency to a sequence within SEQ ID NOs: 1 or 41. In particular, the Examiner states that it is unpredictable what changes in a methionine synthase reductase nucleic acid maintain the activity of the encoded protein.

Applicants respectfully assert that the present claims are fully enabled by the specification. The claimed nucleic acids are useful, for example, in diagnostic methods to detect mutations or polymorphisms associated with altered risk for a disease (see, for example, pages 8-11). In particular, the nucleic acids may be used in standard kits for detecting the presence or absence of any base pair mutation, insertion, or deletion in a mammalian methionine synthase reductase nucleic acid (pages 25 and 26). As disclosed by the applicants, these mutations may be associated with neural tube defects, cancer, or cardiovascular disease (pages 49-57). Subjects identified using these methods as having an increased risk for a disease may be administered a therapeutic agent to prevent or

delay the onset of the disease. Moreover, these nucleic acids may be used as therapeutic antisense nucleic acids to decrease the activity of a mutant methionine synthase reductase polypeptide encoded by a mutant methionine synthase reductase gene in a patient (page 22, lines 14-18).

Given the various substantial clinical uses for these nucleic acids, it would be unfair to limit the present claims to nucleic acids that encode an active methionine synthase reductase protein. However, even if the Examiner is not persuaded that claims 1-5 or 35-44 are enabled, Applicants note that new claims 45 and 46, which require the nucleic acids to encode a polypeptide having at least 20-30% of the biological activity of the methionine synthase reductase polypeptide of SEQ ID NO: 2, clearly recite nucleic acids having substantial utility. Applicants further note that new claim 47, which recites nucleic acids encoding a mammalian methionine synthase reductase polypeptide that has a consensus binding site for FAD, FMN, and/or NADPH, is also directed to useful nucleic acids that maintain the ability to bind a cofactor.

In the interest of expediting prosecution, claim 6 which required the nucleic acid to encode a mutant or polymorphic polypeptide or fragment thereof has been canceled. For the record, applicants do not agree with the present rejection of claim 6 and reserve the right to pursue the canceled subject matter in this or a related continuing application. Accordingly, this rejection should be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 4-6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Leclerc et al. The Examiner asserts that the methionine synthase reductase nucleic acid in which a guanine is replaced by adenine at nucleotide position 66 (SEQ ID NO: 41) or the encoded protein of SEQ ID N0: 42 are not disclosed in parent application U.S.S.N. 09/232,028 and thus are only entitled to the priority of the filing date of the present application. In response to this rejection, applications note that page 46, lines 16-22, of

priority application U.S.S.N. 60/071,622, filed January 16, 1998, state that:

> [t]wo polymorphisms have been identified in methionine synthase reductase cDNAs. The first is a G to A substitution at nucleotide position 66 (66 G to A) using the A of the initiator methionine as nucleotide position number 1 (see Fig. 3). This results in the substitution of isoleucine for methionine at amino acid 22 (M22I). The second polymorphism is a G to A substitution at nucleotide position 110 (110 G to A). This results in the substitution of tyrosine for cysteine at amino acid position 37 (C37Y).

The specification of the priority application further states:

> [i]n another embodiment, the mutation is a point mutation or a deletion mutation, for example, a 4 base deletion starting from base 1675 of SEQ ID NO:1, or a deletion of 3 bases starting from base 1726 of SEQ ID NO:1, or a nucleotide transition from G to A at nucleotide position 66 (SEQ ID NO: 3), or a nucleotide transition from G to A at nucleotide position 110 (SEQ ID NO: 3). Other naturally occurring varients associated with altered risk for hyperhomocysteinemia are also a feature of this aspect of the invention.

Page 5, lines 5-12.

As the nucleic acids of SEQ ID NO: 1, 41, 43, 45, or 47 are disclosed in this priority application, the present claims are entitled to benefit of the priority date of January 16, 1998; which is prior to the March 1988 publication date of Leclerc. As Leclerc can not constitute prior art to these claims, this rejection should be withdrawn.

Claims 4-6 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Hillier et al and under 35 U.S.C. § 102(a) as being anticipated by Strausberg. The Examiner states that Hillier discloses a nucleic acid that hybridizes to nucleotides 1735-2097 of SEQ ID NOs: 1 or 41 with potential mismatches at nucleotides 2067 and 2082 of SEQ ID NOs: 1 or 41 and that Strausberg discloses a nucleic acid that hybridizes to nucleotides 1054 -1407 of SEQ ID NOs: 1 or 41 with no mismatches. As amended, claim 4 (from which claim 5 depends) requires that the nucleic acid which hybridizes at high stringency to SEQ ID NOs: 1 or 41 has a region complementary to a naturally-occurring

mammalian methionine synthase reductase mutation or polymorphism. As recited in new claim 35, in various embodiments the methionine synthase reductase mutation or polymorphism is (i) the alteration from guanine to adenine at nucleotide position 66, (ii) the alteration from guanine to adenine at nucleotide position 110, (iii) the deletion of bases 1675-1678, or (iv) the deletion of bases 1726-1728 relative to SEQ ID NO: 1. As noted above, claim 6 has been cancelled. As Hillier and Strausberg do not disclose a nucleic acid that hybridizes to a methionine synthase reductase mutation or polymorphism, neither Hillier nor Strausberg anticipates claims 4 and 5. Applicants further note that the 366 nucleotide sequence disclosed by Hillier and the 386 nucleotide sequences disclosed by Strausberg do not have at least 50% sequence identity to SEQ ID No.: 1 over the entire length of SEQ ID No.: 1, as required by new claims 36-40. Similarly, the nucleotide sequences disclosed by Hillier and Strausberg do not have a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism, as required by new claims 41-41. Accordingly, these rejections should be withdrawn.

Rejection under 35 U.S.C. § 103

Claim 1 was rejected under 35 U.S.C. § 103 as being unpatentable over Gulati et al. In particular, the Examiner asserts that Gulati teaches that mutations in the auxiliary protein(s) that activates methionine synthase represents an additional locus for genetic defects that can lead to hyperpomoscysteinema and that the individual components await the purification and characterization of these proteins. The Examiner further states that, based on the teachings of Gulati, one skilled in the art would have been motivated to isolate nucleic acids encoding wild-type and mutant mammalian methionine synthase reductase. The Examiner states that these nucleic acids could have been isolated by (i) using chromatography or gel electrophoresis to separate contaminating proteins from a target protein, (ii) obtaining a partial amino acid sequence from the purified protein, (iii)

synthesizing a degenerate probe, (iv) screening a library with the probe to identify a full length nucleic acid, (v) constructing an expression vector comprising the isolated nucleic acid, and (vi) transforming a host cell with the expression vector. Applicants respectfully disagree.

As stated in *Amgen, Inc. v. Chugai Pharmaceutical Col., Ltd*, "obvious to try" is not the proper standard of obviousness under Section 103. Magistrate Sair concluded: "defendants have not demonstrated by clear and convincing evidence that there was a 'reasonable expectation of success' in cloning the EPO gene based on this probing strategy" See, USPQ2d 1737 (D. Mass. 1989), *aff'd in part, rev'd in part, vacated in part*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).

Applicants respectfully assert that the teachings of Gulati are not sufficient to enable the cloning of a mammalian methionine synthase reductase nucleic acid nor provide a reasonable expectation of success for the cloning a mammalian methionine synthase reductase. As stated in on page 19171, third paragraph, of Gulati

> [i]n mammals, intracellular cobalamin is processed *via* a complex multistep pathway..The enzymes involved in this processing pathway remain obscure and have been defined largely by genetic complementation analysis on cells lines from patients with inborn errors of metabolism.

In particular, applicants note that based on the teachings of Gulati, one skilled in the art would appreciate the great level of unpredictability inherent in the isolation of the uncharacterized components postulated by Gulati to be responsible for the activation of mammalian methionine synthase. For example, a skilled artisan would appreciate the isolation of these components in sufficient purity and yield to obtain a partial amino acid sequence of the protein(s) may involve undue experimentation. For example, given the knowledge that the *E. coli* redox activation system uses two proteins, NADPH-flavodoxin reductase and flavodoxin, to shuttle electrons from NADPH to methionine synthase (abstract), one skilled in the art would realize that the activation of mammalian methionine synthase may require two proteins. The existence of two mammalian proteins

responsible for this activity would likely complicate the isolation of the desired proteins. For example, during the purification of the proteins, both proteins would have to be eluted in the same fraction after a chromatography step for the fraction to test positive for the desired redox activity. In addition, the co-eluted proteins would have to be eventually separated from each other in sufficient purity to obtain a partial amino acid sequence of each protein. Not until the applicants' cloning of a mammalian methionine synthase reductase nucleic acid could one skilled in the art establish that the activities of the two *E. coli* redox proteins are in fact contained in one mammalian methionine synthase reductase protein, as disclosed below in the applicants' specification.

> Lower, but still significant homology was found with *E. coli* NADPH-ferredoxin(flavodoxin) reductase (P values > 2x10-9) and flavodoxin (P values > 3x10-2). Our finding suggests a convergent evolution of the two-gene flavodoxin/NADPH-ferredoxin(flavodoxin) reductase system to a single gene encoding a fused version of the two proteins in human cells. Alignment of the proteins provides for a large linker region bridging the two components.

Page 29, lines 1-6.

Even if one skilled in the art were to obtain a partial amino acid sequence of mammalian methionine synthase reductase for use in designing a degenerate primer, the ability of the degenerate primer to hybridize with sufficient stringency and specificity to enable the identification of a mammalian methionine synthase reductase would be highly unpredictable. For example, given the potentially relatively small size of the primer generated from a partial amino acid sequence compared to the full length mammalian methionine synthase reductase nucleic acid (2094 nucleotides) and given the vast number of nucleotide sequences that could encode methionine synthase reductase (4^{2094}), the ability to successfully clone the full length mammalian methionine synthase reductase nucleic acid would be unpredictable. Accordingly, the polynucleotide sequences of the nucleic acids that are disclosed and claimed by the applications can not be considered

obvious in view of Gulati. In particular, as stated in *In re Bell*:

> because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein. In the case of IGF, Bell has argued without contradiction that the Rinderknecht amino acid sequences could be coded for by more than 10^{36} different nucleotide sequences, only a few of which are the human sequences that Bell now claims. Therefore, given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of the possibilities is the human sequence, the claimed sequences would not have been obvious.

See, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993).

As Gulati does not disclose a polynucleotide sequence of a mammalian methionine synthase reductase nucleic acid or provide a reasonable expectation of success in cloning a mammalian methionine synthase reductase nucleic acid based on the limited information available about the complex cobalamin pathway, Gulati can not render the present claims obvious. Accordingly, this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. A marked-up version indicating the amendments made to the claims, as required by 37 C.F.R. § 1.121(c)(1)(ii), is enclosed. Also enclosed is a petition to extend the period for replying for three months, to and including September 5, 2001.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 5, 2001

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Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Roy A. Gravel et al.	Art Unit:	1652
Serial No.:	09/371,347	Examiner:	D. Steadman
Filed:	August 10, 1999	Customer No:	21559

Title: HUMAN METHIONINE SYNTHASE REDUCTASE: CLONING, AND METHODS FOR EVALUATING RISK OF NEURAL TUBE DEFECTS, CARDIOVASCULAR DISEASE, AND CANCER

Assistant Commissioner for Patents
Washington, D.C. 20231

Version with Markings to Show Changes Made

Marked-up versions of claims 1 and 3-5 and new claims 35-47 are presented below.

1. (Amended) A substantially [Substantially] pure nucleic acid encoding a mammalian methionine synthase reductase polypeptide.

3. (Amended) The nucleic acid of claim 1, wherein said nucleic acid has the sequence of SEQ ID NO: 1, [or] SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or

SEQ ID NO: 47, or degenerate variants thereof, and wherein said nucleic acid encodes the amino acid sequence of SEQ ID NO: 2, [or] SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, or SEQ ID NO: 48.

4. (Amended) A substantially pure nucleic acid that hybridizes in 2X SSC medium at 40°C [at high stringency] to a sequence found within [the nucleic acid of] SEQ ID NO: 1 or SEQ ID NO: 41, wherein said nucleic acid comprises a region complementary to a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism.

5. (Amended) The nucleic acid of claim 4, wherein said nucleic acid has a sequence complementary to at least 50% of at least 60 contiguous nucleotides of SEQ ID NO: 1 or SEQ ID NO: 41 [the nucleic acid encoding the methionine synthase reductase polypeptide, said sequence sufficient to allow nucleic acid hybridization under high stringency conditions].

35. (New) The nucleic acid of claim 4, wherein said mutation or polymorphism is an alteration relative to SEQ ID NO: 1 selected from the group consisting of:

a) the alteration from guanine to adenine at nucleotide position 66;

b) the alteration from guanine to adenine at nucleotide position 110;

c) the deletion of bases 1675-1678; and

d) the deletion of bases 1726-1728.

36. (New) A substantially pure nucleic acid having a polynucleotide sequence that has at least 50% sequence identity to SEQ ID No.: 1 over the entire length of SEQ ID No.: 1.

37. (New) The nucleic acid of claim 36, having a polynucleotide sequence that has at least 85% sequence identity to SEQ ID No.: 1 over the entire length of SEQ ID No.: 1.

38. (New) The nucleic acid of claim 37, having a polynucleotide sequence that has at least 95% sequence identity to SEQ ID No.: 1 over the entire length of SEQ ID No.: 1.

39. (New) The nucleic acid of claim 36, comprising a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism.

40. (New) The nucleic acid of claim 39, wherein said mutation or polymorphism is an alteration relative to SEQ ID NO: 1 selected from the group consisting of:

a) the alteration from guanine to adenine at nucleotide position 66;

b) the alteration from guanine to adenine at nucleotide position 110;

c) the deletion of bases 1675-1678; and

d) the deletion of bases 1726-1728.

41. (New) A substantially pure nucleic acid having a polynucleotide sequence that has at least 50% sequence identity to the corresponding region of SEQ ID No.: 1, wherein said nucleic acid comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism.

42. (New) The nucleic acid of claim 41, having a polynucleotide sequence that has at least 85% sequence identity to the corresponding region of SEQ ID No.: 1.

43. (New) The nucleic acid of claim 42, having a polynucleotide sequence that has at least 95% sequence identity to the corresponding region of SEQ ID No.: 1.

44. (New) The nucleic acid of claim 41, wherein said mutation or polymorphism is an alteration relative to SEQ ID NO: 1 selected from the group consisting of:

a) the alteration from guanine to adenine at nucleotide position 66;

b) the alteration from guanine to adenine at nucleotide position 110;

c) the deletion of bases 1675-1678; and

d) the deletion of bases 1726-1728.

45. (New) The nucleic acid of claim 1, 36, or 41, encoding a mammalian methionine synthase reductase polypeptide having at least 20-30% of the ability to catalyze the reductive methylation of methionine synthase-cob(II)alamin to generate methionine synthase-cob(III)alamin-CH3 as the methionine synthase reductase polypeptide of SEQ ID NO: 2.

46. (New) The nucleic acid of claim 45, encoding a mammalian methionine synthase reductase polypeptide having at least 55-75% of the ability to catalyze the reductive methylation of methionine synthase-cob(II)alamin to generate methionine synthase-cob(III)alamin-CH3 as the methionine synthase reductase polypeptide of SEQ ID NO: 2.

47. (New) The nucleic acid of claim 1, 36, or 41, encoding a mammalian methionine synthase reductase polypeptide that comprises a consensus binding site for one or more cofactors selected from the group consisting of FAD, FMN, and NADPH.